Research report

Modal subcomponents of metabolic syndrome in patients with bipolar disorder [☆]

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Abstract

Background: The metabolic syndrome is a growing global public health problem.
Objective: To evaluate the prevalence rate and modal subcomponents of the metabolic syndrome in subjects treated at the West Los Angeles Veterans Administration Medical Center Bipolar Clinic.
Methods: In this cross-sectional design study, using the National Cholesterol Education Program definition, metabolic syndrome prevalence rates were calculated.
Results: 48/98 (49%) of subjects met criteria for metabolic syndrome. There was no difference in prevalence rate by gender or race. Almost 70% of the cohort met criteria for metabolic syndrome by the components of reduced HDL and increased waist circumference. Treatment with carbamazepine at study entry was associated with a lower prevalence rate of metabolic syndrome.
Limitations and conclusions: This study is limited by its small size and non-structured assessment of Axis I diagnosis. Nonetheless, bipolar patients in this select cohort have high rates of metabolic syndrome; given this cardiovascular risk, close clinical monitoring for these parameters is recommended. While not controlling for genetics, environmental influences, and/or medical factors such as additional comorbidity and treatment duration, psychotropic drug use may confer differential risk for developing the metabolic syndrome.
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1. Introduction

The increasing prevalence rate of metabolic syndrome clearly highlights that this is a major global public health problem. The metabolic syndrome is composed of a number of risk factors including insulin resistance, abdominal obesity, dyslipidemia, and hypertension and is associated with an increase in morbidity

and mortality. Utilizing the National Cholesterol Education Program (NCEP) definition of metabolic syndrome, the National Health and Nutrition Examination Survey (NHANES) recently reported that the age-adjusted prevalence rate of metabolic syndrome had increased from 24 to 27% in less than 10 years (Ford et al., 2004).

The increasing prevalence of metabolic syndrome is important because it confers greater cardiovascular morbidity and mortality. Prospective observational studies have demonstrated an association between metabolic syndrome and development of type II diabetes (Hanson et al., 2002; Resnick et al., 2003; Klein et al., 2002; Sattar et al., 2003), cardiovascular disease (Lakka et al., 2002; Kip et al., 2004), and stroke (Kurl et al., 2006).

Given increased attention to atypical antipsychotics and weight gain liability, most of the metabolic syndrome research in psychiatric illness has focused on schizophrenia. In the CATIE study, the metabolic syndrome prevalence rate was 40.9% (McEvoy et al., 2005); CATIE males and females were 138% and 251%, respectively, more likely than their NHANES counterparts to have the metabolic syndrome. Only one small study ($n=171$) by Fagiolini et al. (2005) reported a metabolic syndrome prevalence rate of 30% among subjects with bipolar disorder.

The etiology associated with this increased risk of obesity and metabolic syndrome in bipolar disorder is unknown. In addition to psychosocial factors, increasing concern has focused on the association between second generation antipsychotics, weight gain, and the subsequent risk of dyslipidemia and/or diabetes. The American Diabetes Association and American Psychiatric Association consensus has suggested that these antipsychotics vary in the risk they confer for weight gain and subsequent risk for diabetes and dyslipidemia with clozapine and olanzapine conferring the greatest risk, followed by risperidone and quetiapine, and finally by aripiprazole and ziprasidone (ADA and APA Consensus Conference, 2004). The atypical syndrome of depression, often observed in bipolar disorder, characterized by hypersomnia, carbohydrate hyperphagia, psychomotor retardation, combined with poor diet, and concurrent medication treatment may further increase the risk of developing the metabolic syndrome.

Given the potential for increased risk in patients with bipolar disorder, this study sets out to determine the prevalence of the metabolic syndrome in subjects with bipolar disorder with particular interest in the component criteria of metabolic syndrome and concurrent psychotropic drug treatment.

2. Methods

The study was conducted at the West Los Angeles Veterans Administration Health Care System (WLA VA) Bipolar Clinic and was approved by the WLA VA institutional review board. Written informed consent was obtained on all subjects participating in the study. This cross-sectional study was conducted from November 2004 to May 2006. All subjects receiving care at the clinic with a diagnosis of bipolar disorder type I or II were invited to participate. Diagnosis was determined by clinical evaluation in the clinic by the senior research psychiatrists (MAF or SLM). On study entry, data collected for each subject included: demographic information, current mood state, and psychotropic drug use history within the last 12 months. Current treatment for hypertension, diabetes, or dyslipidemia was confirmed by review of the medical record. Objective data gathered on initial visit included height, weight, body mass index (reference range BMI: 18.5–24.9=healthy, 25–29.9=overweight, 30–40=obese, >40=very obese), waist circumference at the umbilicus (a measure of central adiposity), and blood pressure. Patients were subsequently instructed to have a fasting blood draw to evaluate fasting serum glucose, glycosylated hemoglobin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. Subjects had their blood drawn at the West Los Angeles VA laboratory. On their return visit, subjects received the results from the above blood exams, were educated about their metabolic syndrome status, and compensated twenty dollars. Subjects who met criteria for metabolic syndrome were provided with education and written materials on strategies for healthy living, including diet and exercise.

The National Cholesterol Education Program (NCEP) definition was used to define the metabolic syndrome for this study (Expert Panel JAMA, 2001). The presence of 3 or more of the following criteria was required to meet criteria for metabolic syndrome: fasting glucose ≥ 110 mg/dL, HDL < 40 mg/dL (men) or < 50 mg/dL (women), triglycerides ≥ 150 mg/dL, blood pressure ≥ 130/ ≥ 85 mm Hg, and waist circumference (measured at the umbilicus) > 40 in. (102 cm, men) or > 35 in. (88 cm, women).

The metabolic syndrome categories were further divided into subjects who were receiving treatment for component criteria (i.e. were taking medications (Rx) to treat hypertension, dyslipidemia, or diabetes) and those who were not. Thus 4 categories were evaluated: 1.) subjects who did not meet criteria for metabolic syndrome (MetSyn) and were not on treatment for component criteria [MetSyn(−)Rx(−)], 2.) subjects who

did not meet criteria for the metabolic syndrome but were on treatment for component criteria [MetSyn(−)Rx (+)], 3.) subjects who did meet criteria for the metabolic syndrome and were not on treatment for component criteria [MetSyn(+)Rx(−)], and 4.) subjects who did meet criteria for the metabolic syndrome and were on treatment for component criteria [MetSyn(+)Rx(+)].

Baseline demographics and prevalence rate of metabolic syndrome by age, gender, race, and psychotropic drug use were analyzed by *t*-test and chi square. Means and standard deviations are reported for all continuous variables and frequencies for categorical variables. A 2×2 analysis of variance (ANOVA) was completed on each clinical value evaluating potential differences between MetSyn(+) vs. MetSyn(−) subjects, Rx(+) vs. Rx(−) subjects, and the interaction between metabolic syndrome and medication status. Log transformation was done for the glucose and triglyceride data given its non-parametric distribution. Although there was limited ability given the small number of women ($n=8$), Asian ($n=4$), and Latinos ($n=7$), possible confounds of age, gender, and race on the prevalence rate of metabolic syndrome were explored utilizing logistic regression.

3. Results

A total of 107 subjects enrolled in the study. Of these, 98 subjects (60 Caucasians, 27 African Americans, 7 Latinos, and 4 Asians) had complete laboratory and clinical data for analysis. There were 90 males (mean age 49.9 ± 10.2 years) and 8 females (51.6 ± 8.4. years). The overall prevalence of metabolic syndrome was 49% and did not differ by gender (males=48.9% vs. females= 50%, $X^2=0.004$, $df=1$, $p=0.95$) or by racial group (Caucasian=55%, African American=44%, Latino= 29%, Asian=25%, $X^2=3.18$, $df=3$, $p=0.36$). The mean age of subjects who met criteria for metabolic syndrome was significantly older (52.1 ± 9.2 years) than the mean age of those subjects who did not meet criteria (48 ± 10.4 years, $t=2.05$, $df=96$, $p=0.04$). Logistic regression analysis showed an effect of age (Wald $X^2=3.96$, $df=1$, $p<0.05$), but not gender (Wald $X^2=0.004$, $df=1$, $p= 0.95$), or race (Wald $X^2=3.02$, $df=3$, $p=0.39$) on prevalence rates of metabolic syndrome.

Table 1 shows the mean (+/−SD) clinical measures and subcomponents of the metabolic syndrome of the entire cohort and by MetSyn and Rx status. Subjects with MetSyn(+) status, in comparison to MetSyn(−) status, had significantly higher measurements on serum glucose, glycosylated hemoglobin, serum triglycerides, waist, and BMI and a significantly lower level of HDL. Subjects who were Rx(+), in comparison to those subjects who were Rx (−), had a significantly lower level of total cholesterol and significantly higher level of glycosylated hemoglobin. All groups had a BMI in the range of obesity (>30) with the exception of MetSyn(−) and MetSyn(−)/Rx(−) subjects.

Table 1
Mean (+/−SD) clinical values and subcomponents of metabolic syndrome

	Cohort	Metabolic syndrome(−)	Metabolic syndrome(+)	Metabolic syndrome (−)/treatment(−)	Metabolic syndrome(−)/ treatment(+)	Metabolic syndrome(+)/ treatment(−)	Metabolic syndrome(+)/ treatment(+)
	N=98	N=50	N=48	N=32	N=18	N=19	N=29
*Glucose**	*101.1 (27.7)*	*90.6 (15.6)*	*111.9 (33.1)*	*90.1 (16.9)*	*91.5 (13.4)*	*103 (15.8)*	*117.8 (39.8)*
Glycosylated hemoglobin*^	5.7 (0.9)	5.5 (0.4)	6 (1.1)	5.4 (0.4)	5.6(0.5)	5.5(0.4)	6.3(1.3)
Total cholesterol^	196.8 (44.6)	196.9 (44.3)	196.6 (45.3)	204.8 (44.8)	182.9 (40.7)	208.4 (53.5)	188.9 (38.1)
Low-density lipoprotein	119 (40.1)	124.4 (37.0)	113.3 (42.8)	129.8 (39.5)	114.7 (31)	116.4 (44.2)	111.3 (42.5)
*High-density lipoprotein**	*41.2 (12.1)*	*47.7(12.1)*	*34.5 (7.5)*	*48.9 (12.9)*	*45.5 (10.5)*	*33.2 (8.6)*	*35.3 (6.8)*
*Triglycerides**	*184.8 (128.6)*	*126.5 (61.6)*	*244.3 (150.8)*	*132.4 (66.7)*	*116.3 (52)*	*291.3 (190.8)*	*213.4 (110.7)*
Systolic blood pressure	*124.2 (14.4)*	*121.7 (12.8)*	*127 (15.5)*	*118.7 (11.9)*	*127.1 (13)*	*126.8 (15.1)*	*127.4 (15.9)*
Diastolic blood pressure	*78.5 (10.4)*	*77.5 (10.3)*	*80 (10.6)*	*76.4 (9.0)*	*79.6 (12.2)*	*78.8 (9.1)*	*80.7 (11.5)*
*Waist**	*42.9 (5.5)*	*40.1 (5.1)*	*45.9 (4.1)*	*39.3 (5.2)*	*41.3 (4.9)*	*45.3 (4.1)*	*46.2 (4.1)*
Body mass index category*	31.9 (5.3) obese	29.6 (4.2) overweight	34.3 (5.2) obese	28.9 (3.7) overweight	30.9 (4.8) obese	34.5 (6.9) obese	34.1 (4.0) obese

NCEP(National Cholesterol Education Program) subcomponents are *italicized*.
*Significant difference by metabolic syndrome (MetSyn) (+) vs. MetSyn(−) status, ^significant difference by Rx(+) vs. Rx(−) status, *log glucose (MetSyn status: $df=1,97$, $F=15.67$, $p=0.0001$; Rx status: $F=1.81$, $p=0.18$; MetSyn*Rx $F=0.75$, $p=0.39$), *^Hb A1C (MetSyn status: $df=1,96$, $F=4.54$, $p=0.04$; Rx status: $F=8.82$, $p=0.004$; MetSyn*Rx $F=2.24$, $p=0.14$), ^TChol (MetSyn status: $df=1,97$, $F=0.27$, $p=0.6$; Rx status: $F=5.08$, $p<0.03$; MetSyn*Rx=$F=0.02$, $p=0.89$), *HDL (MetSyn status: $df=1,97$, $F=37.8$, $p<0.0001$; Rx status: $F=0.1$, $p=0.75$; MetSyn*Rx=$F=1.71$, $p=0.19$), *log TG (MetSyn status: $df=1,96$, $F=41.8$, $p<0.0001$; Rx status: $F=3.2$, $p=0.08$, MetSyn*Rx: $F=0.54$, p 0.5), *waist (MS status: 1,97, $F=15.3$, $p=0.0002$; Rx status: $F=1.0$, $p=0.32$; MetSyn*Rx: $F=0.87$, $p=0.35$), *BMI (MetSyn status: $df=1,97$, $F=20.33$, $p<0.0001$; Rx status: $F=0.7$, $p=0.4$; MetSyn*Rx: $F=1.53$, $p=0.2$).
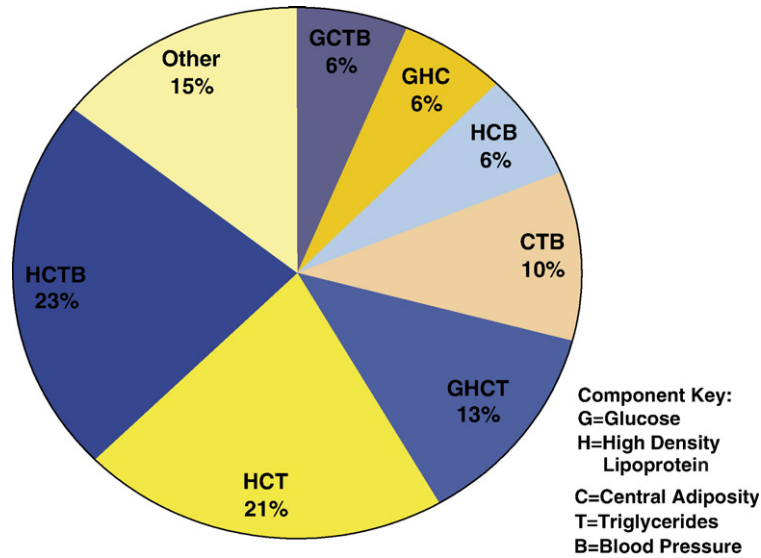
Fig. 1. Component frequencies for subjects meeting criteria for metabolic syndrome ($N=48$).

Almost 60% of the cohort met criteria for metabolic syndrome by the components of reduced HDL, increased waist circumference, and elevated triglycerides and almost 70% of the cohort met criteria for metabolic syndrome by the components of reduced HDL and increased waist circumference (see Fig. 1).
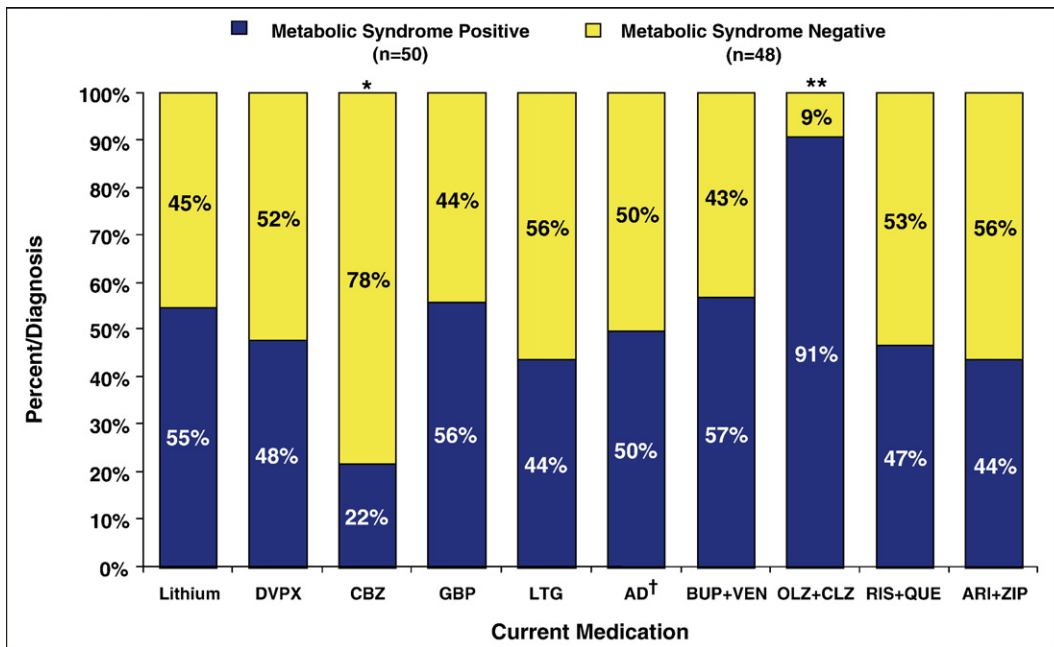
Fig. 2. Medications by metabolic syndrome (MS) status.

Psychotropic medications at study entry were also examined by metabolic syndrome status (see Fig. 2). There were statistically more subjects on olanzapine or clozapine at study entry who met criteria for metabolic syndrome than those who did not ($X^2 = 14.73$ $p = 0.0001$). Conversely, there were statistically more subjects on carbamazepine at study entry who did not meet criteria for metabolic syndrome than those who did ($X^2 = 5.56$ $p < 0.02$).

4. Discussion

The prevalence of the metabolic syndrome in bipolar subjects seeking treatment at the West Los Angeles VA Bipolar clinic was 49%. Although the studies have different sampling and designs, making formal comparison difficult, this prevalence rate was higher than that found in the CATIE schizophrenia study and nearly twice that found in the general population. However, the small sample size of our study and particularly women in this study is a significant limitation and makes study conclusions related to gender differences difficult. We did not find different rates among the different racial groups; again, the small sample size of the Asian and Latino subgroups is a significant limitation of this study. There is a suggestion in the literature that definitions of overall obesity and abdominal obesity in Asian populations should be based on lower waist circumference cut off points (Patel et al., 2006; Tan et al., 2004; WHO Expert Consultation, 2004). Application of a modified metabolic syndrome definition for Asian populations may be justified and may provide different results in our study. This study did find that older age was a factor in the prevalence rate of metabolic syndrome in this VA patient cohort.

The subdivision of subjects into those who are metabolic syndrome positive vs. negative and to those receiving treatment vs. not receiving treatment for the component criteria is, to our knowledge in previous bipolar research, unique. These data suggest the possibility of a treatment effect of lowering total cholesterol, regardless of metabolic syndrome status. Conversely, the linear increase in glucose and hemoglobin A1c would seem to indicate the lack of medication effect in regard to the regulation of glucose. It is difficult to draw definitive conclusions as the specific medication for treatment of the specific component criteria was not analyzed. Nonetheless, these results are particularly noteworthy, given that the ability to treat insulin resistance with drugs that enhance insulin action has not yet been shown to improve clinical outcomes compared to weight reduction and exercise (Meigs, 2003; Knowler et al., 2002). The main therapeutic goal in patients with the metabolic syndrome

is prevention or reduction of obesity, and more specifically abdominal obesity (Manson et al., 2004). This is best achieved through the combination of diet (the Mediterranean diet has been shown to improve endothelial function and lipid profiles), exercise (a daily minimum of 30 min of moderate intensity physical activity), and possibly pharmacologic therapy (Reaven et al., 2001; Heymsfield et al., 2000; Esposito et al., 2004; Despres et al., 1991).

Examining how our subjects most frequently met criteria for the metabolic syndrome also yielded an interesting result with most qualifying for the syndrome with the combination of reduced HDL and central adiposity as measured by increased waist circumference (with or without additional component criteria). Such information can be clinically useful in monitoring for the metabolic syndrome. A previous study found that abdominal obesity was most sensitive (92%) while fasting glucose >100 mg/dL was most specific (95.2%) in correctly identifying the presence of the metabolic syndrome and combining both gave a 100% sensitivity (Straker et al., 2005).

Finally, the present study yielded information on psychotropic drug use as it relates to the metabolic syndrome, an area that will need further study. The present study did not control for baseline indices such as additional psychiatric comorbidity, presence of concurrent risk factors, family history, socioeconomic status, length of time on psychotropic treatment, or number of potentially weight liable medications subjects were taking. Yet, a number of findings suggest that further research is warranted. First, subjects on olanzapine or clozapine were more likely to be metabolic syndrome positive. This finding is consistent with previous findings that novel atypical antipsychotics and particularly clozapine and olanzapine are associated with weight gain, elevated glucose and disturbed lipid values (Wirshing et al., 2002). Secondly, subjects on carbamazepine were less likely to meet criteria for the metabolic syndrome. This finding may represent the lowered weight gain liability associated with carbamazepine or pharmacokinetic factors specific to this medication. Carbamazepine is a potent inducer of CYP3A4 and other oxidative enzyme systems in the liver, and it may also increase glucuronyl transferase activity; the net effect is an acceleration of the metabolism of concurrently prescribed medications lowering their levels, and thus lowering possible untoward side effects such as lipid and glucose disturbance (Spina et al., 1996). Carbamazepine also increases lipid levels including HDL. This effect may mean that patients who otherwise might have met criteria for the metabolic syndrome through low HDL may escape the designation. This is

particularly salient given a recent finding that while total cholesterol and high-density lipoprotein concentrations increased after 2 months of treatment with carbamazepine and remained high after 1 and 5 years, the concentrations of serum LDL cholesterol and triglycerides only increased transiently during the first year of medication treatment (Isojarvi et al., 1993).

The present study has several limitations most notably the small sample size and lack of structured diagnostic interview to confirm a bipolar diagnosis and subtype pattern. Furthermore, a selection bias cannot be ruled out as not all patients in our clinic were study participants; this cohort represents about 25% of our patient population and outside of time constraints for study participation, there may be clinical factors in this cohort that may not generalize to other patients with bipolar disorder. Despite the fact that our population was made up of a fairly homogenous population, mainly male veterans, we did not obtain specific information on treatment (i.e. dose duration of treatment) for component criteria and therefore could not perform a subanalysis of the effect of medications for hypertension, diabetes, and dyslipidemia on the metabolic syndrome. Also, in the analysis of psychotropic drug use as it relates to the presence of the metabolic syndrome, we did not control for baseline indices of illness severity (both cross-sectional and longitudinal) or length of psychotropic drug treatment. The sample size for each drug, even the atypical antipsychotics that were combined for analysis similar to the APA/ADA consensus statement, was small and larger studies will need to be done to confirm these preliminary observations.

In summary, almost 50% of our bipolar patient population met criteria for metabolic syndrome. We found a possible effect of concurrent treatment for component criteria of the metabolic syndrome. Finally, there was an association with psychotropic drug therapy; patients on olanzapine or clozapine were more likely and patients on carbamazepine were less likely respectively to have the metabolic syndrome.

Conflict of interest

Mark A. Frye M.D. Disclosure Declaration 2006

Consultant

Abbott Laboratories, Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly and Co., GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson PRD, Novartis, Ortho McNeil, Otsuka Pharmaceuticals, Pfizer Inc., Shire Pharmaeuticals, Solvay Pharmaceuticals, Wyeth

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